

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

1-75 (Canceled)

76. (Previously Presented) A composition, comprising:

- a metal;
- a chelator capable of chelating the metal;
- an indazole nonpeptide targeting moiety covalently bound to the chelator, either directly or via an optional interposed linking group, wherein the targeting moiety binds to a receptor that is upregulated during angiogenesis; and
- at least one of a chemotherapeutic agent or a radiosensitizer agent.

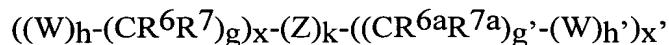
77. (Previously Presented) The composition of claim 76, wherein the metal, targeting moiety, chelator, and optional linking group are a diagnostic or therapeutic metallopharmaceutical.

78. (Previously Presented) The composition of claim 76, wherein the chemotherapeutic agent is mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminogluthethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, or leutinizing hormone releasing factor.

79. (Previously Presented) The composition of claim 76, wherein the radiosensitizer agent is 2-(3-nitro-1,2,4-triazol-1-yl)-N-(2-methoxyethyl)acetamide, N-(3-nitro-4-quinoliny)-4-morpholinecarboxamidine, 3-amino-1,2,4-benzotriazine-1,4-dioxide, N-(2-hydroxyethyl)-2-nitroimidazole-1-acetamide, 1-(2-nitroimidazol-1-yl)-3-(1-piperidiny)-2-propanol, or 1-(2-nitro-1-imidazolyl)-3-(1-aziridino)-2-propanol.

80. (Previously Presented) The composition of claim 76, wherein the linking group is present between the targeting moiety and the chelator.

81. (Previously Presented) The composition of claim 76, wherein the linking group has a formula:



wherein:

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, NR<sup>8</sup>C(=O), C(=O)NR<sup>8</sup>, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO<sub>2</sub>, SO<sub>2</sub>NH, (OCH<sub>2</sub>CH<sub>2</sub>)<sub>20-200</sub>, (CH<sub>2</sub>CH<sub>2</sub>O)<sub>20-200</sub>, (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>20-200</sub>, (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O)<sub>20-200</sub>, and (aa)<sub>t</sub>;

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R<sup>10</sup>, C<sub>3-10</sub> cycloalkyl substituted with 0-3 R<sup>10</sup>, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R<sup>10</sup>;

R<sup>6</sup>, R<sup>6a</sup>, R<sup>7</sup>, R<sup>7a</sup>, and R<sup>8</sup> are independently selected at each occurrence from the group: H, =O, COOH, SO<sub>3</sub>H, PO<sub>3</sub>H, C<sub>1</sub>-C<sub>5</sub> alkyl substituted with 0-3 R<sup>10</sup>, aryl substituted with 0-3 R<sup>10</sup>, benzyl substituted with 0-3 R<sup>10</sup>, and C<sub>1</sub>-C<sub>5</sub> alkoxy substituted with 0-3 R<sup>10</sup>, NHC(=O)R<sup>11</sup>, C(=O)NHR<sup>11</sup>, NHC(=O)NHR<sup>11</sup>, NHR<sup>11</sup>, R<sup>11</sup>, and a bond to the chelator;

$R^{10}$  is independently selected at each occurrence from the group: a bond to the chelator,  $COOR^{11}$ ,  $C(=O)NHR^{11}$ ,  $NHC(=O)R^{11}$ , OH,  $NHR^{11}$ ,  $SO_3H$ ,  $PO_3H$ ,  $-OPO_3H_2$ ,  $-OSO_3H$ , aryl substituted with 0-3  $R^{11}$ ,  $C_{1-5}$  alkyl substituted with 0-1  $R^{12}$ ,  $C_{1-5}$  alkoxy substituted with 0-1  $R^{12}$ , and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3  $R^{11}$ ;

$R^{11}$  is independently selected at each occurrence from the group: H, alkyl substituted with 0-1  $R^{12}$ , aryl substituted with 0-1  $R^{12}$ , a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1  $R^{12}$ ,  $C_{3-10}$  cycloalkyl substituted with 0-1  $R^{12}$ , and a bond to the chelator;

$R^{12}$  is a bond to the chelator;

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, and 2;

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

x is selected from 0, 1, 2, 3, 4, and 5; and

x' is selected from 0, 1, 2, 3, 4, and 5.

82. (Previously Presented) The composition of claim 76, wherein the receptor is  $\alpha_v\beta_3$  or  $\alpha_v\beta_5$ .

83. (Previously Presented) The composition of claim 76, wherein the metal is  $^{99m}Tc$ ,  $^{95}Tc$ ,  $^{111}In$ ,  $^{62}Cu$ ,  $^{64}Cu$ ,  $^{67}Ga$ , or  $^{68}Ga$ .

84. (Previously Presented) The composition of claim 76, wherein the metal is  $^{99m}Tc$  or  $^{95}Tc$ .

85. (Previously Presented) The composition of claim 76, wherein the metal is  $^{99m}Tc$ .

86. (Previously Presented) The composition of claim 76, wherein the metal is  $^{111}\text{In}$ .

87. (Previously Presented) The composition of claim 76, further comprising a first ancillary ligand and a second ancillary ligand.

88. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:

$^{99\text{m}}\text{Tc}$  (((4-(4-(((3-(2-(2-(3-((6-(diazenido)(3-pyridyl))carbonylamino)propoxy)ethoxy)ethoxy)propyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)propanoic acid) (tricine)(TPPTS);

$^{99\text{m}}\text{Tc}$  (2-(2-((5-(N-(1,3-bis(3-(2-(2-(3-(((4-(4-(((1-carboxy-2-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)ethyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)propyl)carbamoyl)(2-pyridyl))2-diazenido) (tricine)(TPPTS);

$^{99\text{m}}\text{Tc}$  (2-((6-(diazenido)(3-pyridyl))carbonylamino)-4-(N-(3-(2-(2-(3-(((4-(4-(((1-carboxy-2-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)ethyl)amino)sulfonyl)phenyl)phenyl)sulfonyl)amino)propoxy)ethoxy)ethoxy)propyl)carbamoyl)butanoic acid) (tricine)(TPPTS);

$^{99\text{m}}\text{Tc}$  (2-(6-((6-(diazenido)(3-pyridyl))carbonylamino)hexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)-propanoic acid) (tricine)(TPPTS);

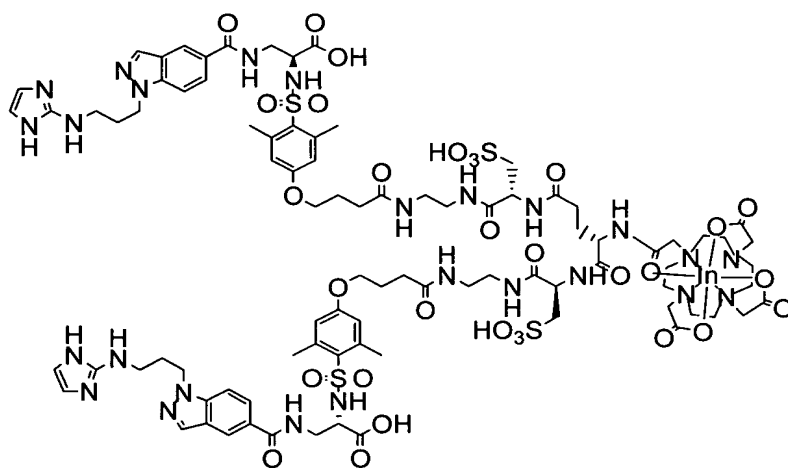
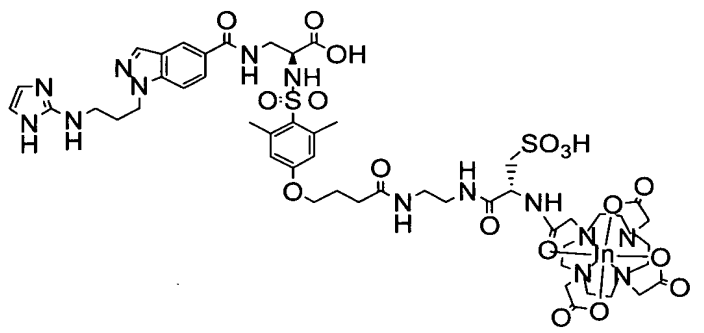
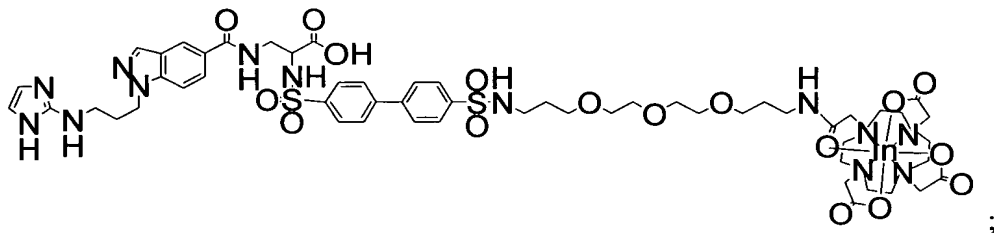
$^{99\text{m}}\text{Tc}$  (2-((6-(diazenido)(3-pyridyl))carbonylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonylamino)propanoic acid (tricine)(TPPTS);

$^{99\text{m}}\text{Tc}$  [2-[[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid)(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid)) (tricine)(TPPTS); or

$^{99\text{m}}\text{Tc}$  ([2-[[[5-[carbonyl]-2-pyridinyl]diazenido]-Glu-bis-[Glu(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-

amino)propanoic acid)(2-(6-aminohexanoylamino)-3-((1-(3-(imidazol-2-ylamino)propyl)(1H-indazol-5-yl))carbonyl-amino)propanoic acid))] (tricine)(TPPTS).

89. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:

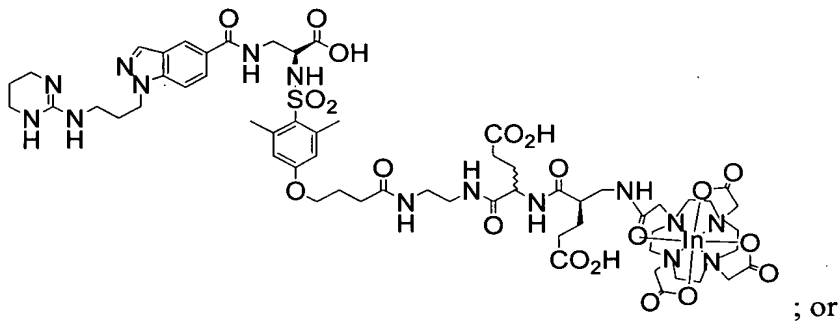
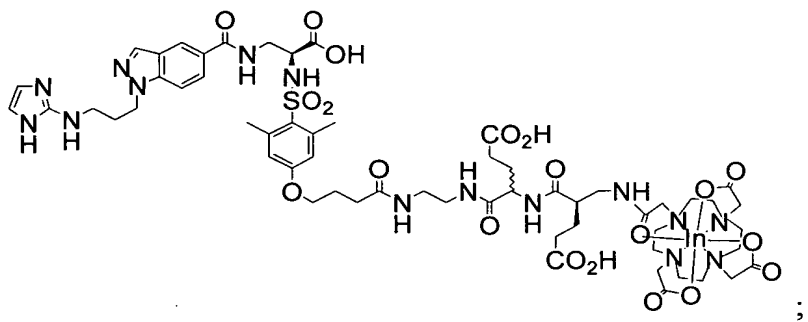
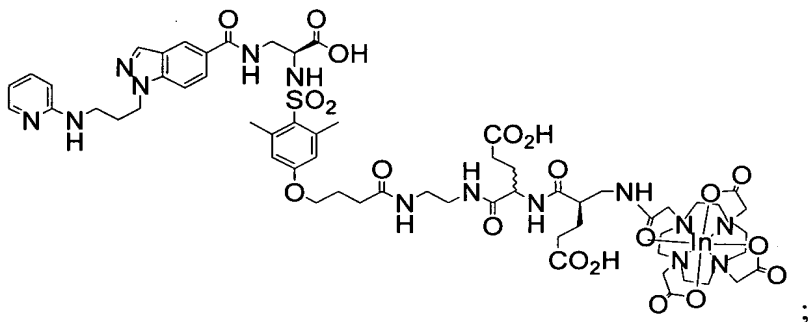
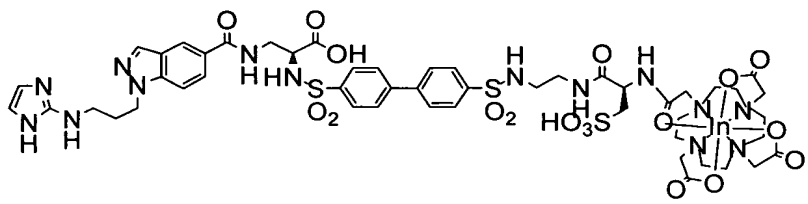


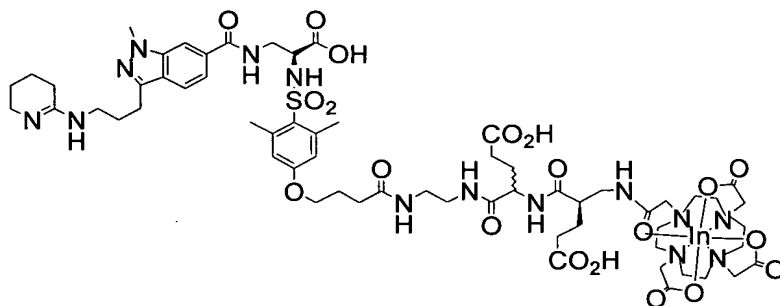
DOCKET NO.: BMS-0690 (DM-6999-A)

Application No.: 09/599,890

Office Action Dated: September 9, 2005

PATENT





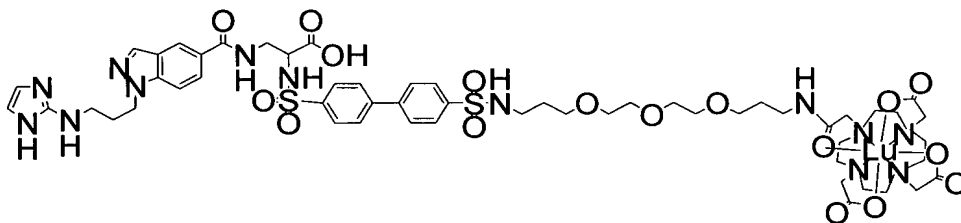
90. (Previously Presented) The composition of claim 76, wherein the metal is <sup>33</sup>P, <sup>125</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>153</sup>Sm, <sup>166</sup>Ho, <sup>177</sup>Lu, <sup>149</sup>Pm, <sup>90</sup>Y, <sup>212</sup>Bi, <sup>103</sup>Pd, <sup>109</sup>Pd, <sup>159</sup>Gd, <sup>140</sup>La, <sup>198</sup>Au, <sup>199</sup>Au, <sup>169</sup>Yb, <sup>175</sup>Yb, <sup>165</sup>Dy, <sup>166</sup>Dy, <sup>67</sup>Cu, <sup>105</sup>Rh, <sup>111</sup>Ag, or <sup>192</sup>Ir.

91. (Previously Presented) The composition of claim 76, wherein the metal is <sup>153</sup>Sm.

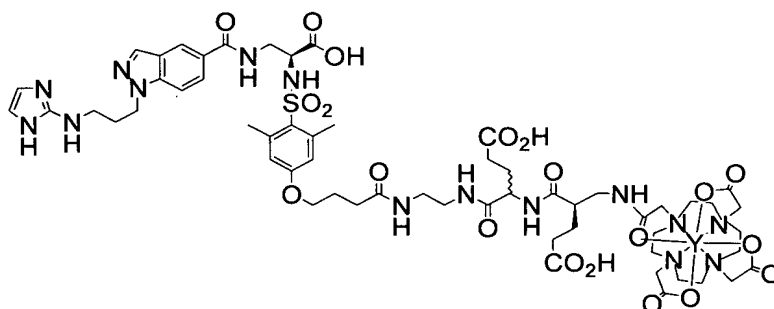
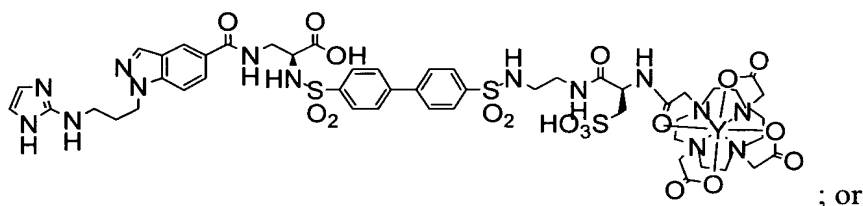
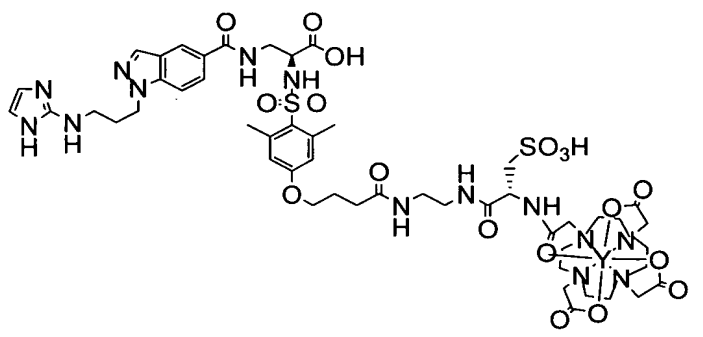
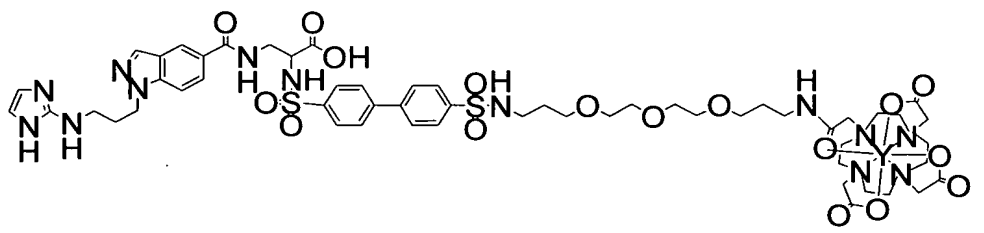
92. (Previously Presented) The composition of claim 76, wherein the metal is <sup>177</sup>Lu.

93. (Previously Presented) The composition of claim 76, wherein the metal is <sup>90</sup>Y.

94. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:



95. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:



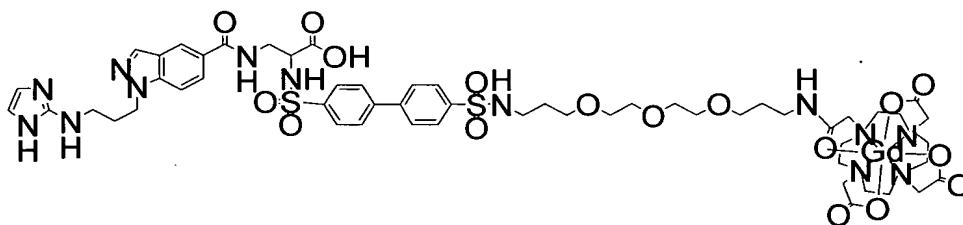
96. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is a MRI contrast agent, the metal is a paramagnetic metal ion selected from the group: Gd(III), Dy(III), Fe(III), and Mn(II), and the linking group is present between the targeting moiety and chelator.



97. (Previously Presented) The composition of claim 96, wherein the receptor is  $\alpha_v\beta_3$  or  $\alpha_v\beta_5$ .

98. (Previously Presented) The composition of claim 96, wherein the metal ion is Gd(III).

99. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is:



100. (Previously Presented) The composition of claim 77, wherein the metallopharmaceutical is a X-ray contrast agent, the metal is selected from the group: Re, Sm, Ho, Lu, Pm, Y, Bi, Pd, Gd, La, Au, Au, Yb, Dy, Cu, Rh, Ag, and Ir, the receptor is  $\alpha_v\beta_3$  or  $\alpha_v\beta_5$ , and the linking group is present between the targeting moiety and chelator.

101. (Previously Presented) A composition, comprising:

an indazole nonpeptide targeting moiety attached to a surfactant via a linking group, wherein the targeting moiety binds to a receptor that is upregulated during angiogenesis; and an echogenic gas.

102. (Previously Presented) The composition of claim 101, wherein the receptor is  $\alpha_v\beta_3$  or  $\alpha_v\beta_5$ .

103. (Previously Presented) The composition of claim 102, wherein the surfactant is a lipid

or a compound of the formula:  $A^9-E^1-A^{10}$ ; wherein

$A^9$  is selected from the group: OH and OR<sup>27</sup>;

A<sup>10</sup> is OR<sup>27</sup>;

R<sup>27</sup> is C(=O)C<sub>1-20</sub> alkyl;

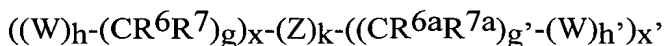
E<sup>1</sup> is C<sub>1-10</sub> alkylene substituted with 1-3 R<sup>28</sup>;

R<sup>28</sup> is independently selected at each occurrence from the group: R<sup>30</sup>, -PO<sub>3</sub>H-R<sup>30</sup>, =O, -CO<sub>2</sub>R<sup>29</sup>, -C(=O)R<sup>29</sup>, -C(=O)N(R<sup>29</sup>)<sub>2</sub>, -CH<sub>2</sub>OR<sup>29</sup>, -OR<sup>29</sup>, -N(R<sup>29</sup>)<sub>2</sub>, C<sub>1-5</sub> alkyl, and C<sub>2-4</sub> alkenyl;

R<sup>29</sup> is independently selected at each occurrence from the group: R<sup>30</sup>, H, C<sub>1-6</sub> alkyl, phenyl, benzyl, and trifluoromethyl;

R<sup>30</sup> is a bond to the linking group.

104. (Previously Presented) The composition of claim 103, wherein the linking group has a formula:



wherein:

W is independently selected at each occurrence from the group: O, S, NH, NHC(=O), C(=O)NH, NR<sup>8</sup>C(=O), C(=O)NR<sup>8</sup>, C(=O), C(=O)O, OC(=O), NHC(=S)NH, NHC(=O)NH, SO<sub>2</sub>, SO<sub>2</sub>NH, (OCH<sub>2</sub>CH<sub>2</sub>)<sub>20-200</sub>, (CH<sub>2</sub>CH<sub>2</sub>O)<sub>20-200</sub>, (OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>20-200</sub>, (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O)<sub>20-200</sub>, and (aa)<sub>t'</sub>;

aa is independently at each occurrence an amino acid;

Z is selected from the group: aryl substituted with 0-3 R<sup>10</sup>, C<sub>3-10</sub> cycloalkyl substituted with 0-3 R<sup>10</sup>, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R<sup>10</sup>;

R<sup>6</sup>, R<sup>6a</sup>, R<sup>7</sup>, R<sup>7a</sup>, and R<sup>8</sup> are independently selected at each occurrence from the group: H, =O, COOH, SO<sub>3</sub>H, PO<sub>3</sub>H, C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>10</sup>, aryl substituted

with 0-3 R<sup>10</sup>, benzyl substituted with 0-3 R<sup>10</sup>, and C<sub>1</sub>-C<sub>5</sub> alkoxy substituted with 0-3 R<sup>10</sup>, NHC(=O)R<sup>11</sup>, C(=O)NHR<sup>11</sup>, NHC(=O)NHR<sup>11</sup>, NHR<sup>11</sup>, R<sup>11</sup>, and a bond to S<sub>f</sub>,

R<sup>10</sup> is independently selected at each occurrence from the group: a bond to S<sub>f</sub>, COOR<sup>11</sup>, C(=O)NHR<sup>11</sup>, NHC(=O)R<sup>11</sup>, OH, NHR<sup>11</sup>, SO<sub>3</sub>H, PO<sub>3</sub>H, -OPO<sub>3</sub>H<sub>2</sub>, -OSO<sub>3</sub>H, aryl substituted with 0-3 R<sup>11</sup>, C<sub>1-5</sub> alkyl substituted with 0-1 R<sup>12</sup>, C<sub>1-5</sub> alkoxy substituted with 0-1 R<sup>12</sup>, and a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-3 R<sup>11</sup>;

R<sup>11</sup> is independently selected at each occurrence from the group: H, alkyl substituted with 0-1 R<sup>12</sup>, aryl substituted with 0-1 R<sup>12</sup>, a 5-10 membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O and substituted with 0-1 R<sup>12</sup>, C<sub>3-10</sub> cycloalkyl substituted with 0-1 R<sup>12</sup>, and a bond to S<sub>f</sub>,

R<sup>12</sup> is a bond to S<sub>f</sub>,

k is selected from 0, 1, and 2;

h is selected from 0, 1, and 2;

h' is selected from 0, 1, and 2;

g is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

g' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

t' is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

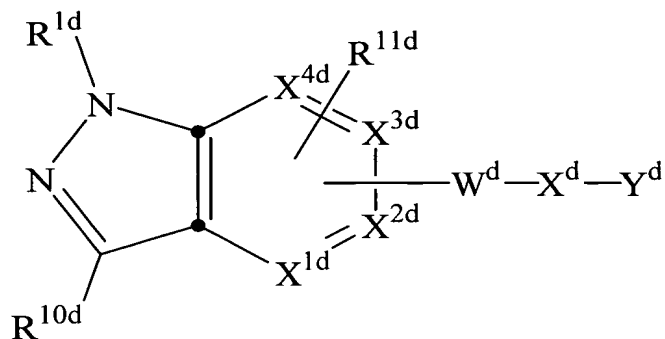
x is selected from 0, 1, 2, 3, 4, and 5; and

x' is selected from 0, 1, 2, 3, 4, and 5.

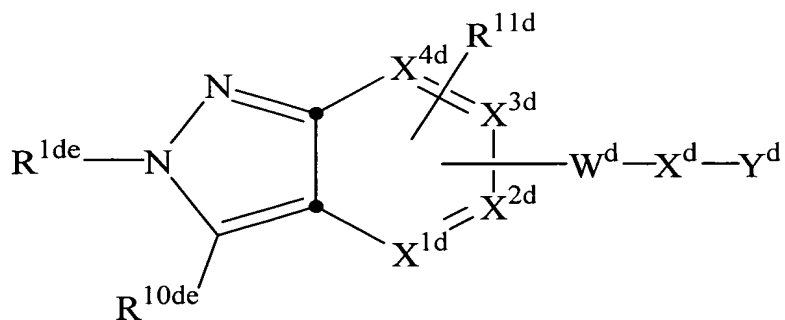
105. (Previously Presented) The composition of claim 104, further comprising: 1,2-dipalmitoyl-sn-glycero-3-phosphatidic acid, 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine, and N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine.

106. (Previously Presented) The composition of claim 105, wherein the echogenic gas is a C<sub>2-5</sub> perfluorocarbon.

107. (Currently Amended) The composition of claim 76 or claim 101, wherein the indazole nonpeptide is a compound of Formulae (Ia) or (Ib):



(Ia)



(Ib)

~~including stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof,~~  
~~or pharmaceutically acceptable salt or prodrug forms thereof,~~  
 wherein:

X<sup>1d</sup> is CH, C- W<sup>d</sup>- X<sup>d</sup>- Y<sup>d</sup>, or C bonded to the linking group;

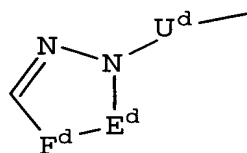
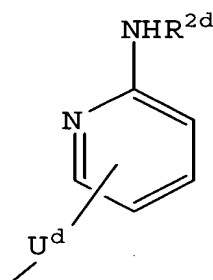
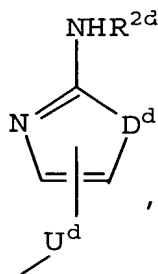
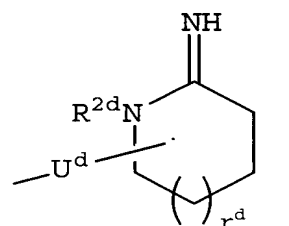
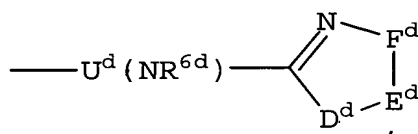
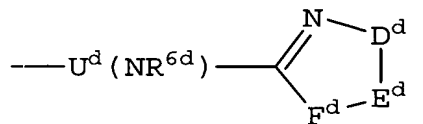
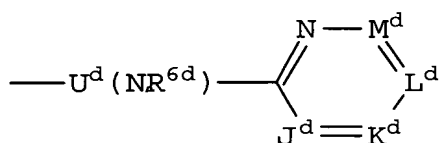
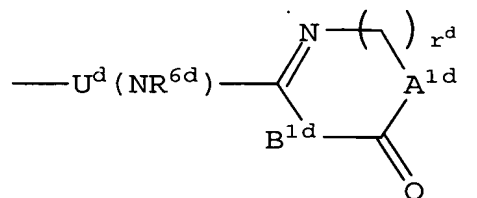
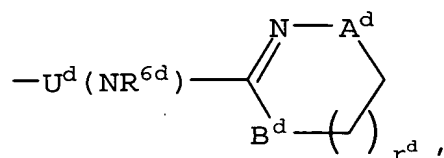
X<sup>2d</sup> is CH or C- W<sup>d</sup>- X<sup>d</sup>- Y<sup>d</sup>;

X<sup>3d</sup> is CR<sup>11d</sup> or C- W<sup>d</sup>- X<sup>d</sup>- Y<sup>d</sup>;

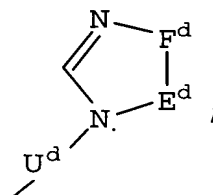
X<sup>4d</sup> is CR<sup>11d</sup>;

$R^{1d}$  is selected from:  $R^{1de}$ , C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>3</sub>-C<sub>6</sub> alkenyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , aryl substituted with 0-1  $R^{15d}$  or 0-2  $R^{11d}$  or 0-1  $R^{21d}$ , and aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)- substituted with 0-1  $R^{15d}$  or 0-2  $R^{11d}$  or 0-1  $R^{21d}$ ;

$R^{1de}$  is selected from:



or



$A^d$  and  $B^d$  are independently  $-\text{CH}_2-$ ,  $-\text{O}-$ ,  $-\text{N}(\text{R}^{2d})-$ , or  $-\text{C}(=\text{O})-$ ;

A<sup>1d</sup> and B<sup>1d</sup> are independently -CH<sub>2</sub>- or -N(R<sup>3d</sup>)-;

D<sup>d</sup> is -N(R<sup>2d</sup>)-, -O-, -S-, -C(=O)- or -SO<sub>2</sub>-;

E<sup>d</sup>-F<sup>d</sup> is -C(R<sup>4d</sup>)=C(R<sup>5d</sup>)-, -N=C(R<sup>4d</sup>)-, -C(R<sup>4d</sup>)=N-, or -C(R<sup>4d</sup>)<sub>2</sub>C(R<sup>5d</sup>)<sub>2</sub>-;

J<sup>d</sup>, K<sup>d</sup>, L<sup>d</sup> and M<sup>d</sup> are independently selected from:

-C(R<sup>4d</sup>)-, -C(R<sup>5d</sup>)- and -N-, provided that at least one of J<sup>d</sup>, K<sup>d</sup>, L<sup>d</sup> and M<sup>d</sup> is not -N-;

provided that when R<sup>1d</sup> is R<sup>1de</sup> then one of X<sup>1d</sup> and X<sup>2d</sup> is C- W<sup>d</sup>- X<sup>d</sup>- Y<sup>d</sup>, and when R<sup>10d</sup> is R<sup>1de</sup> then X<sup>3d</sup> is C- W<sup>d</sup>- X<sup>d</sup>- Y<sup>d</sup>;

R<sup>2d</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkyl, (C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)carbonyl; (C<sub>1</sub>-C<sub>6</sub> alkyl)aminocarbonyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl, aryl, heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl, heteroarylcarbonyl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl-, arylcarbonyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, arylsulfonyl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)sulfonyl, heteroarylsulfonyl, heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)sulfonyl, aryloxycarbonyl, and aryl(C<sub>1</sub>-C<sub>6</sub> alkoxy)carbonyl, wherein said aryl groups are substituted with 0-2 substituents selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo, CF<sub>3</sub>, and nitro;

R<sup>3d</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, and heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sup>4d</sup> and R<sup>5d</sup> are independently selected from: H, C<sub>1</sub>-C<sub>4</sub> alkoxy, NR<sup>2d</sup>R<sup>3d</sup>, halogen, NO<sub>2</sub>, CN, CF<sub>3</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, (C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl, (C<sub>1</sub>-C<sub>6</sub> alkoxy)carbonyl, arylcarbonyl, or

alternatively, when substituents on adjacent atoms, R<sup>4d</sup> and R<sup>5d</sup> can be taken together with the carbon atoms to which they are attached to form a 5-7 membered carbocyclic or 5-7 membered heterocyclic aromatic or non-aromatic ring system, said carbocyclic or heterocyclic ring being optionally substituted with 0-2 groups selected from: C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halo, cyano, amino, CF<sub>3</sub>, and NO<sub>2</sub>;

U<sup>d</sup> is selected from:

-(CH<sub>2</sub>)<sub>n</sub><sup>d</sup>-,

$-(CH_2)_n^d(CR^{7d}=CR^{8d})(CH_2)_m^d-$ ,  
 $-(CH_2)_n^d(C\equiv C)(CH_2)_m^d-$ ,  
 $-(CH_2)_t^dJ^d(CH_2)_m^d-$ ,  
 $-(CH_2)_n^dO(CH_2)_m^d-$ ,  
 $-(CH_2)_n^dN(R^{6d})(CH_2)_m^d-$ ,  
 $-(CH_2)_n^dC(=O)(CH_2)_m^d-$ ,  
 $-(CH_2)_n^d(C=O)N(R^{6d})(CH_2)_m^d-$ ,  
 $-(CH_2)_n^dN(R^{6d})(C=O)(CH_2)_m^d-$ , and  
 $-(CH_2)_n^dS(O)_p^d(CH_2)_m^d-$ ;

wherein one or more of the methylene groups in  $U^d$  is optionally substituted with  $R^{7d}$ ;

$J^d$  is selected from 1,2-cycloalkylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 2,3-pyridinylenes, 3,4-pyridinylenes, 2,4-pyridinylenes, and 3,4-pyridazinylenes;

$R^{6d}$  is selected from: H, C<sub>1</sub>-C<sub>4</sub> alkyl, or benzyl;

$R^{7d}$  and  $R^{8d}$  are independently selected from: H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, and heteroaryl(C<sub>0</sub>-C<sub>6</sub> alkyl)-;

$R^{10d}$  is selected from: H,  $R^{1de}$ , C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-1  $R^{21d}$ ,  $N(R^{6d})_2$ , halogen, NO<sub>2</sub>, CN, CF<sub>3</sub>, CO<sub>2</sub> $R^{17d}$ , C(=O) $R^{17d}$ , CONR<sup>17d</sup> $R^{20d}$ , -SO<sub>2</sub> $R^{17d}$ , -SO<sub>2</sub>NR<sup>17d</sup> $R^{20d}$ , C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>3</sub>-C<sub>6</sub> alkenyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl substituted with 0-1  $R^{15d}$  or 0-1  $R^{21d}$ , aryl substituted with 0-1  $R^{15d}$  or 0-2  $R^{11d}$  or 0-1  $R^{21d}$ , and aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)- substituted with 0-1  $R^{15d}$  or 0-2  $R^{11d}$  or 0-1  $R^{21d}$ ;

$R^{10de}$  is selected from: H, C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-1  $R^{21d}$ ,  $N(R^{6d})_2$ , halogen, NO<sub>2</sub>, CN, CF<sub>3</sub>, CO<sub>2</sub> $R^{17d}$ , C(=O) $R^{17d}$ , CONR<sup>17d</sup> $R^{20d}$ , -SO<sub>2</sub> $R^{17d}$ , -



SO<sub>2</sub>NR<sup>17d</sup>R<sup>20d</sup>, C<sub>1</sub>-C<sub>6</sub> alkyl substituted with 0-1 R<sup>15d</sup> or 0-1 R<sup>21d</sup>, C<sub>3</sub>-C<sub>6</sub> alkenyl substituted with 0-1 R<sup>15d</sup> or 0-1 R<sup>21d</sup>, C<sub>3</sub>-C<sub>7</sub> cycloalkyl substituted with 0-1 R<sup>15d</sup> or 0-1 R<sup>21d</sup>, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl substituted with 0-1 R<sup>15d</sup> or 0-1 R<sup>21d</sup>, aryl substituted with 0-1 R<sup>15d</sup> or 0-2 R<sup>11d</sup> or 0-1 R<sup>21d</sup>, and aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)- substituted with 0-1 R<sup>15d</sup> or 0-2 R<sup>11d</sup> or 0-1 R<sup>21d</sup>;

R<sup>11d</sup> is selected from H, halogen, CF<sub>3</sub>, CN, NO<sub>2</sub>, hydroxy, NR<sup>2d</sup>R<sup>3d</sup>, C<sub>1</sub>-C<sub>4</sub> alkyl substituted with 0-1 R<sup>21d</sup>, C<sub>1</sub>-C<sub>4</sub> alkoxy substituted with 0-1 R<sup>21d</sup>, aryl substituted with 0-1 R<sup>21d</sup>, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)- substituted with 0-1 R<sup>21d</sup>, (C<sub>1</sub>-C<sub>4</sub> alkoxy)carbonyl substituted with 0-1 R<sup>21d</sup>, (C<sub>1</sub>-C<sub>4</sub> alkyl)carbonyl substituted with 0-1 R<sup>21d</sup>, C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl substituted with 0-1 R<sup>21d</sup>, and C<sub>1</sub>-C<sub>4</sub> alkylaminosulfonyl substituted with 0-1 R<sup>21d</sup>;

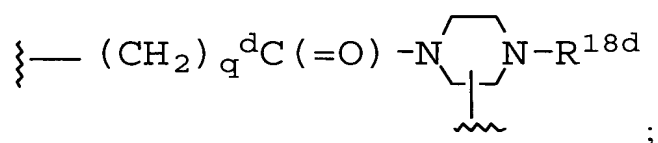
W<sup>d</sup> is selected from:

-(C(R<sup>12d</sup>)<sub>2</sub>)<sub>q</sub><sup>d</sup>C(=O)N(R<sup>13d</sup>)-, and

-C(=O)-N(R<sup>13d</sup>)-(C(R<sup>12d</sup>)<sub>2</sub>)<sub>q</sub><sup>d</sup>-;

X<sup>d</sup> is -C(R<sup>12d</sup>)(R<sup>14d</sup>)-C(R<sup>12d</sup>)(R<sup>15d</sup>)-, or

alternatively, W<sup>d</sup> and X<sup>d</sup> can be taken together to be



R<sup>12d</sup> is selected from H, halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>10</sub> cycloalkylalkyl, (C<sub>1</sub>-C<sub>4</sub> alkyl)carbonyl, aryl, and aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sup>13d</sup> is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkylmethyl, and aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sup>14d</sup> is selected from:

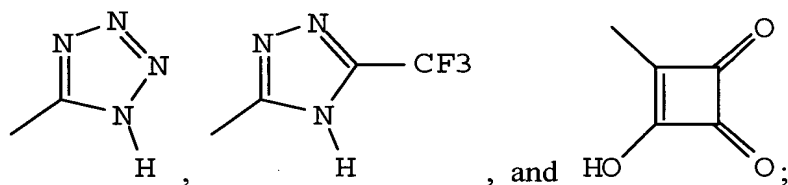
H, C<sub>1</sub>-C<sub>6</sub> alkylthio(C<sub>1</sub>-C<sub>6</sub> alkyl)-, aryl(C<sub>1</sub>-C<sub>10</sub> alkylthioalkyl)-, aryl(C<sub>1</sub>-C<sub>10</sub> alkoxyalkyl)-, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>6</sub> hydroxyalkyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkylalkyl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, aryl, heteroaryl, CO<sub>2</sub>R<sup>17d</sup>, C(=O)R<sup>17d</sup>, and CONR<sup>17d</sup>R<sup>20d</sup>, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-1 R<sup>16d</sup> or 0-2 R<sup>11d</sup>;

R<sup>15d</sup> is selected from:

H, R<sup>16d</sup>, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>1</sub>-C<sub>10</sub> alkoxyalkyl, C<sub>1</sub>-C<sub>10</sub> alkylaminoalkyl, di(C<sub>1</sub>-C<sub>10</sub> alkyl)aminoalkyl, (C<sub>1</sub>-C<sub>10</sub> alkyl)carbonyl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)carbonyl, C<sub>2</sub>-C<sub>10</sub> alkenyl, C<sub>2</sub>-C<sub>10</sub> alkynyl, C<sub>3</sub>-C<sub>10</sub> cycloalkyl, C<sub>3</sub>-C<sub>10</sub> cycloalkylalkyl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, aryl, heteroaryl, CO<sub>2</sub>R<sup>17d</sup>, C(=O)R<sup>17d</sup>, CONR<sup>17d</sup>R<sup>20d</sup>, SO<sub>2</sub>R<sup>17d</sup>, and SO<sub>2</sub>NR<sup>17d</sup>R<sup>20d</sup>, provided that any of the above alkyl, cycloalkyl, aryl or heteroaryl groups may be unsubstituted or substituted independently with 0-2 R<sup>11d</sup>;

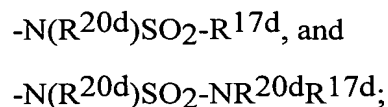
Y<sup>d</sup> is selected from:

-COR<sup>19d</sup>, -SO<sub>3</sub>H, -PO<sub>3</sub>H, tetrazolyl, -CONHNHSO<sub>2</sub>CF<sub>3</sub>, -CONHSO<sub>2</sub>R<sup>17d</sup>, -CONHSO<sub>2</sub>NHR<sup>17d</sup>, -NHCOCF<sub>3</sub>, -NHCONHSO<sub>2</sub>R<sup>17d</sup>, -NHSO<sub>2</sub>R<sup>17d</sup>, -OPO<sub>3</sub>H<sub>2</sub>, -OSO<sub>3</sub>H, -PO<sub>3</sub>H<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>2</sub>NHCOR<sup>17d</sup>, -SO<sub>2</sub>NHCO<sub>2</sub>R<sup>17d</sup>,



R<sup>16d</sup> is selected from:

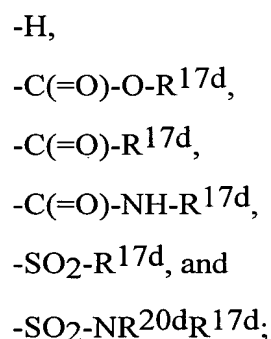
-N(R<sup>20d</sup>)-C(=O)-O-R<sup>17d</sup>,  
-N(R<sup>20d</sup>)-C(=O)-R<sup>17d</sup>,  
-N(R<sup>20d</sup>)-C(=O)-NH-R<sup>17d</sup>,



$R^{17d}$  is selected from:

$C_1$ - $C_{10}$  alkyl optionally substituted with a bond to the linking group,  $C_3$ - $C_{11}$  cycloalkyl optionally substituted with a bond to the linking group, aryl( $C_1$ - $C_6$  alkyl)- optionally substituted with a bond to the linking group, ( $C_1$ - $C_6$  alkyl)aryl optionally substituted with a bond to the linking group, heteroaryl( $C_1$ - $C_6$  alkyl)- optionally substituted with a bond to the linking group, ( $C_1$ - $C_6$  alkyl)heteroaryl optionally substituted with a bond to the linking group, biaryl( $C_1$ - $C_6$  alkyl)- optionally substituted with a bond to the linking group, heteroaryl optionally substituted with a bond to the linking group, aryl optionally substituted with a bond to the linking group, biaryl optionally substituted with a bond to the linking group, and a bond to the linking group, wherein said aryl, biaryl or heteroaryl groups are also optionally substituted with 0-3 substituents selected from the group:  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy, aryl, heteroaryl, halo, cyano, amino,  $CF_3$ , and  $NO_2$ ;

$R^{18d}$  is selected from:



$R^{19d}$  is selected from: hydroxy,  $C_1$ - $C_{10}$  alkyloxy,  $C_3$ - $C_{11}$  cycloalkyloxy, aryloxy, aryl( $C_1$ - $C_6$  alkoxy)-,  $C_3$ - $C_{10}$  alkylcarbonyloxyalkyloxy,  $C_3$ - $C_{10}$  alkoxy carbonyloxyalkyloxy,  $C_2$ - $C_{10}$  alkoxy carbonylalkyloxy,  $C_5$ - $C_{10}$  cycloalkylcarbonyloxyalkyloxy,  $C_5$ - $C_{10}$  cycloalkoxy carbonyloxyalkyloxy,  $C_5$ - $C_{10}$  cycloalkoxy carbonylalkyloxy,  $C_7$ - $C_{11}$  aryloxy carbonylalkyloxy,  $C_8$ - $C_{12}$  aryloxy carbonyloxyalkyloxy,  $C_8$ - $C_{12}$  arylcarbonyloxyalkyloxy,  $C_5$ - $C_{10}$

alkoxyalkylcarbonyloxyalkyloxy, C<sub>5</sub>-C<sub>10</sub> (5-alkyl-1,3-dioxo-cyclopenten-2-one-yl)methyloxy, C<sub>10</sub>-C<sub>14</sub> (5-aryl-1,3-dioxo-cyclopenten-2-one-yl)methyloxy, and

(R<sup>11d</sup>)(R<sup>12d</sup>)N-(C<sub>1</sub>-C<sub>10</sub> alkoxy)-;

R<sup>20d</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl, C<sub>4</sub>-C<sub>11</sub> cycloalkylalkyl, aryl, aryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-, and heteroaryl(C<sub>1</sub>-C<sub>6</sub> alkyl)-;

R<sup>21d</sup> is selected from: COOH and NR<sup>6d</sup><sub>2</sub>;

m<sup>d</sup> is 0-4;

n<sup>d</sup> is 0-4;

t<sup>d</sup> is 0-4;

p<sup>d</sup> is 0-2;

q<sup>d</sup> is 0-2; and

r<sup>d</sup> is 0-2;

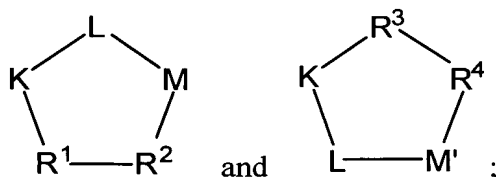
with the following provisos:

(1) t<sup>d</sup>, n<sup>d</sup>, m<sup>d</sup> and q<sup>d</sup> are chosen such that the number of atoms connecting R<sup>1d</sup> and Y<sup>d</sup> is in the range of 10-14; and

(2) n<sup>d</sup> and m<sup>d</sup> are chosen such that the value of n<sup>d</sup> plus m<sup>d</sup> is greater than one unless U<sup>d</sup> is

-(CH<sub>2</sub>)<sub>t</sub><sup>d</sup> J<sup>d</sup> (CH<sub>2</sub>)<sub>m</sub><sup>d</sup>; or

Q is a peptide selected from the group:



$R^1$  is L-valine, D-valine or L-lysine optionally substituted on the  $\epsilon$  amino group with a bond to the linking group;

$R^2$  is L-phenylalanine, D-phenylalanine, D-1-naphthylalanine, 2-aminothiazole-4-acetic acid or tyrosine, the tyrosine optionally substituted on the hydroxy group with a bond to the linking group;

$R^3$  is D-valine;

$R^4$  is D-tyrosine substituted on the hydroxy group with a bond to the linking group;

provided that one of  $R^1$  and  $R^2$  in each Q is substituted with a bond to the linking group, and further provided that when  $R^2$  is 2-aminothiazole-4-acetic acid, K is N-methylarginine;

d is selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10;

108. (Previously Presented) A therapeutic composition, comprising:  
the composition of claim 76 and a parenterally acceptable carrier.

109. (Previously Presented) A diagnostic composition, comprising:  
the composition of claim 76 and a parenterally acceptable carrier.

110. (Previously Presented) An ultrasound contrast agent composition, comprising:  
composition of claim 101 and a parenterally acceptable carrier.